Notice of Allowability	Application No.	Applicant(s)	
	10/590,823	SHIOZAWA ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *2/1/10*.

2. ☒ The allowed claim(s) is/are *7-10,13 and 14*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *3/22/10* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Gary Tanigawa on March 22, 2010.

The application has been amended as follows:

The claims have been amended to read:

7. A method for determining whether a human subject has developed rheumatoid arthritis or has the likelihood of developing rheumatoid arthritis, comprising:

(i) detecting whether CpG sequences in a region from base 374 to base 592 of SEQ ID NO: 1 in a DR3 gene promoter region obtained from synovial cells or synovial infiltrating lymphocytes of the human subject are methylated or not; and

(ii) determining that the human subject has developed rheumatoid arthritis or has the likelihood of developing rheumatoid arthritis when there is an increase in the number of methylated CpG sequences in the region from base 374 to base 592 of SEQ ID NO: 1 are methylated as compared to a control DR3 gene promoter region from base 374 to base 592 of SEQ ID NO: 1.

8. A method as set forth in Claim 7, wherein (i) comprises:

a DNA converting step of converting unmethylated cytosines to uracils in CpG sequences contained in the DR3 gene promoter region obtained from the synovial cells

or synovial infiltrating lymphocytes by treating the DR3 gene promoter region with a bisulfite-containing reagent;

a DNA amplifying step of amplifying the DR3 gene promoter region, after the treatment in the DNA converting step, by a polymerase chain reaction using methylation-specific primers or unmethylation-specific primers;

a methylation-state detecting step of detecting how many CpG sequences are methylated, by detecting whether the polymerase chain reaction in the DNA amplifying step using the methylation-specific primers or the unmethylation-specific primers has amplified the DR3 gene promoter region; and

a comparing step of comparing the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating lymphocytes with the DR3 gene promoter region obtained from the peripheral blood lymphocytes, in regard to the methylation state of the DR3 gene promoter regions detected in the methylation-state detecting step, or a confirming step of confirming that the DR3 promoter region obtained from the synovial cells or synovial infiltrating lymphocytes is strongly methylated.

9. A method for determining whether a human subject has developed rheumatoid arthritis or has a likelihood of developing rheumatoid arthritis, comprising:

detecting whether CpG sequences from base 374 to base 592 of SEQ ID NO: 1 in a DR3 gene promoter region obtained from synovial cells or synovial infiltrating lymphocytes of a human subject are methylated or not;

detecting whether CpG sequences from base 374 to base 592 of SEQ ID NO: 1 in a DR3 gene promoter region obtained from peripheral blood lymphocytes of the human subject are methylated or not;

comparing methylation of the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating lymphocytes with methylation of the DR3 gene promoter region obtained from the peripheral blood lymphocytes; and

determining that the human subject has developed rheumatoid arthritis or has the likelihood of developing rheumatoid arthritis when the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating lymphocytes is methylated at a higher ratio than the DR3 gene promoter region obtained from the peripheral blood lymphocytes.

10. A method for determining whether a human subject has developed rheumatoid arthritis or has a likelihood of developing rheumatoid arthritis, comprising:

detecting whether CpG sequences from base 374 to base 592 of SEQ ID NO: 1 in a DR3 gene promoter region obtained from synovial cells or synovial infiltrating lymphocytes of a human subject are methylated or not;

comparing methylation of the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating lymphocytes with a control DR3 gene promoter region obtained from peripheral blood lymphocytes of a healthy human subject; and

determining that the human subject has developed rheumatoid arthritis or has the likelihood of developing rheumatoid arthritis when the DR3 gene promoter region obtained from the synovial cells or synovial infiltrating lymphocytes is methylated at a

higher ratio than the DR3 gene promoter region originating in the peripheral blood lymphocytes of the healthy human subject.

13. A method as set forth in claim 8, wherein the methylation-specific primers and the unmethylation-specific primers are designed to amplify at least the nucleotide sequence from base 374 to base 564 of SEQ ID NO: 1.

14. A method as set forth in claim 8, wherein:

the methylation-specific primers consist of SEQ ID NOS: 2 and 3, respectively, and

the unmethylation-specific primers consist of SEQ ID NOS: 4 and 5, respectively.

The title has been amended to read:

--Methods for Diagnosing Rheumatoid Arthritis--

The following is an examiner's statement of reasons for allowance:

A. The prior rejection of claims 7-10 under 35 USC 102(b) has been obviated by the filing of the translations of JP priority documents 2004-297965, 2004-247525, 2004-112548 and 2004-052495, which establish priority of the claimed invention prior to the publication date of the Takami (September 2004) reference.

B. The closest prior art of Takami et al (25 November 2003; cited in the IDS of 8/25/06) teaches the results of a DNA methylation analysis of the DR3 promoter. Takami reports that allele-specific methylation occurred in the CpG region of 380-180bp upstream of the translation start site and that CpG regions downstream were

unmethylated. It is stated that based on the methylation results, it is possible that DR3 may be subject to genomic imprinting and that future research will focus on studying the effect of methylation on RA. However, Takami does not specifically teach the methylation status of the DR3 gene promoter in DR3 nucleic acids obtained from synovial cells or synovial infiltrating lymphocytes and does not specifically teach that an increase in the methylation of the DR3 gene promoter in DR3 nucleic acids obtained from synovial cells or synovial infiltrating lymphocytes as compared to peripheral blood lymphocytes is indicative of risk of developing RA. Accordingly, the claims are allowable over the prior art because the prior art does not teach or suggest the presently claimed methods for determining whether a human subject has or is at risk of developing rheumatoid arthritis by determining the methylation status of CpG sequences in a region from base 374-592 of SEQ ID NO: 1 in a DR3 gene promoter region obtained from synovial cells or synovial infiltrating lymphocytes and determining that a human subject has developed or has the likelihood of developing rheumatoid arthritis if there is an increase in methylation of the CpG sequences as compared to a control DR3 gene promoter region from base 374-592 of SEQ ID NO: 1, or as compared to the DR3 gene promoter from base 374-592 obtained from peripheral blood lymphocytes from the human subject or from a healthy human subject.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634